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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of STEINMAN *et al.*

Atty. Docket No. ARG010RC

Confirmation No. 9977

Application No. 09/073,596

Art Unit: 1644

Date Filed: 6 May 1998

Examiner: Gerald R. Ewoldt

Title: METHOD FOR IN VITRO PROLIFERATION OF DENDRITIC CELL PRECURSORS
AND THEIR USE TO PRODUCE IMMUNOGENS

REPLY BRIEF

Pursuant to 37 CFR § 41.41, Appellants respond to the Examiner's Answer as follows.

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STATUS OF CLAIMS

The status of claims remains as it was at the time of filing the Appeal Brief; specifically, Claims 99, 101, 103-113, 116, 120 and 142-145 stand rejected and are at issue in this appeal. Claims 1-98, 100, 102, 103, 114, 115, 117-119, and 121-141 were canceled without prejudice or disclaimer.

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GROUND OF REJECTION TO BE REVIEWED ON APPEAL

- A. Was it proper to deny the benefit of the priority claim to the application?
- B. Under 35 U.S.C. § 102(a), was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly anticipated?
- C. Under 35 U.S.C. § 103(a), was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly obvious?
- D. Under 35 U.S.C. § 112, first paragraph, was it proper to reject claims 99, 101, 104-113, 116, 120, and 142-145 as allegedly containing new matter?
- E. Under 35 U.S.C. § 112, second paragraph, was it proper to reject claim 120 as allegedly indefinite?

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ARGUMENTS

Appellants note that this Reply Brief is in response to the Examiner's Answer and is not intended to be a Substitute Brief.

The Examiner's Answer addresses the Grounds of Rejection in a different order than both the Final Rejection and Appellants' Appeal Brief. For the sake of judicial economy, here Appellants first discuss the priority claim because if the Board agrees that the claims are entitled to the filing date of the '612 application, then the cited Pancholi *et al.* (1992) reference is not prior art and the Board need not consider whether it anticipates the claims. The written description rejection involves a similar analysis to the priority claim and so is addressed in the second section.

Priority Claim ("A")

As noted above, if the Board agrees that the claims are entitled to the filing date of the '612 application, the cited Pancholi *et al.* (1992) reference, which published afterwards, is not prior art and the Board need not consider whether the Pancholi reference anticipates the claims.

The section of the Examiner's Answer relating to the priority claim appears to repeat verbatim the text of the same section from the Final Rejection, followed by two new paragraphs. In response to the text repeated from the Final Rejection, Appellants refer to their discussion of this issue in the Appeal Brief. The last (newly added) paragraph in the Examiner's Answer regarding the priority claim alleges that a phrase used in the claims is not found in the specification. In this regard, Appellants submit that the Examiner appears to be applying an improperly heightened standard of written description that requires each claim to be set forth in the specification in its entirety, verbatim.

The proper test for meeting the written description requirement is that the disclosure as originally filed conveys to one skilled in the art that the inventor had possession of the invention, but this does not require "*in haec verba* support for the claimed subject matter...." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000). Rather, all that is required is "reasonable clarity." (MPEP § 2163). The Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

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In this case, neither the Final Rejection nor the Examiner's Answer adequately explains why the passages discussed in the Appeal Brief would not be understood by one of skill in the art to be describing the subject matter of the claims. In contrast to the Examiner's assertions that Appellants are selecting terms out of context, Appellants submit that it is the Examiner who seeks to limit the teachings of the present application by incorrectly interpreting the specification as a series of unrelated statements and by requiring verbatim support for each claim in its entirety.

The current claim terminology was carefully selected in an earnest attempt to address the many and varied written description rejections raised by the Examiner, including, for example, the rejection in the Office Action of August 2, 2007 in which the Examiner objected to the term "dendritic cells" and suggested that the terminology be changed to indicate one of "two distinct cell types, DC precursors and mature DCs." To address this concern, Appellants amended the claims to include the adjective "mature" to clarify that the resulting cells were distinct from the precursor cells also mentioned in the claims. A careful reading of the specification shows that the terms "mature" and "antigen-activated" are both adjectives used to describe properties of cells that can be produced using the methods of the invention. The relationship between the methods of the invention and their use to produce either mature DCs or mature, antigen-activated DCs is made clear, for example, in the Abstract and throughout the specification, for example, in the paragraph bridging pages 9 and 10. As the specification explains, antigen-activated dendritic cells (also referred to, *inter alia*, as dendritic cells expressing modified antigen) are dendritic cells that are prepared according to the methods of the invention and are further (*i.e.*, additionally) treated by exposure to antigen. That is, "[a]ntigen-activated dendritic cells [can be] prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T cells" (specification at page 9, line 35 through page 10, line 3).

In summary, a reading of the specification as a whole and the particular passages cited in the Appeal Brief shows that the specification describes various embodiments of the invention and fully supports the present claims. Corresponding support is also found in the priority application. Accordingly, the benefit of the priority application should be accorded to the present claims and the Board should reverse the denial of the priority claim.

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The other new paragraph of the Examiner's Answer regarding the priority claim indicates that no support has been cited in the '357 application. As discussed in the Appeal Brief, the support for the claims in the '612 application described in Appendix A of the Appeal Brief is also found in every application in the priority chain, including the '357 application and the instant application (No. 09/073,596). This issue was also discussed, for example, in the Amendment filed August 5, 2008, which noted that all support cited in the '612 application is also found in the '357 application. Each application in the priority chain is either a continuation or continuation-in-part and includes at least the information provided in the earlier-filed applications in the chain. In view of this, and because priority to the first-filed ('612) application has been properly claimed, Appellants do not understand why an Examiner would need pinpoint cites for each passage in each application in the priority chain. Appellants respectfully submit that any obligation of providing information in this regard has been met.

35 U.S.C. §112, First Paragraph—Written Description ("D")

The standard for meeting the written description requirement is that the disclosure as originally filed conveys to one skilled in the art that the inventor had possession of the invention at the time of filing, but the disclosure need not provide "*in haec verba* support for the claimed subject matter...." *Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000).

The Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989).

The Examiner's Answer alleges that "[a] review of the cites does not reveal adequate written support for the claimed limitation," which in this instance is the last step of claim 101 and 145 and the corresponding step of claim 120. A detailed discussion of support for all of the claims is set forth in the Appeal Brief and is not repeated here; however, to respond to this particular allegation, specific support for this limitation is highlighted in the table below.

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Claim limitation terms:	Support cited (in the present application):
...for a time sufficient to allow the antigen to bind to the dendritic cells	“The antigen-activated dendritic cells of the invention are produced by exposing antigen, <i>in vitro</i> , to the dendritic cells prepared according to the method of the invention. Dendritic cells are plated in culture dishes and exposed to antigen in a sufficient amount and for a sufficient period of time to allow the antigen to bind to the dendritic cells. ” (page 34, line 34 through page 35, line 3)
and wherein the dendritic cells process the antigen to produce a modified antigen which is expressed by the dendritic cells.	“Foreign and autoantigens are processed by the dendritic cells of the invention to retain their immunogenic form. The immunogenic form implies processing the antigen through fragmentation to produce a form of the antigen that can be recognized by and stimulate T cells.” (page 34, lines 16-20) “Dendritic cells bind and modify antigens in a manner such that the modified antigen when presented on the surface of the dendritic cell can activate T-cells to participate in the eventual production of antibodies.” (page 5, lines 20- 24)

This step is also specifically described in conjunction with the methods of the invention, for example, in original claim 44 of the '357 application (same as original claim 36 of the '612 application), which is as follows:

Original claim 44: “A composition comprising antigen-activated dendritic cells wherein dendritic cells prepared according to claim 17 are pulsed with an antigen and wherein the dendritic cells process the antigen to **produce a modified antigen which is expressed by the dendritic cells.**”

These passages are only part of the support for this claim which is discussed in the Appeal Brief (see, for example, the Summary of Claimed Subject Matter for the instant specification in the Appeal Brief and for the '612 priority application in the chart included with the Appeal Brief as Appendix A). In view of this support, Appellants submit that the written description requirement has been met and respectfully request that the Board reverse this rejection.

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35 U.S.C. §102—Anticipation (“B”)

As noted above, if the Board holds that the priority claim to the ‘612 application is valid, the Pancholi *et al.* (1992) reference (“Pancholi”) cited in the 102 rejection is not prior art. However, in the event that the Board agrees with the Examiner regarding the priority claim, Appellants respectfully submit that the Pancholi reference does not anticipate the claims.

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631 (Fed. Cir. 1987). When assessing the patentability of product-by-process claims over the prior art, **the structure implied by the process steps should be considered, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.** MPEP §2113, citing *In re Garnero*, 412 F.2d 276, 279 (CCPA 1979).

Appellants respectfully submit that in applying the Pancholi reference to the claims, the Examiner appears to be disregarding most of the claim limitations. The present claims specify dendritic cells derived from an *in vitro* culture of proliferating dendritic cell precursors. This is the claimed product. The claims further specify a process by which that product is made. MPEP § 2113, cited in the Examiner’s Answer, clearly states that “determination of patentability is based on the product itself.” Here, the product is not merely dendritic cells, but dendritic cells arising from a specific type of culture. Moreover, the Examiner appears to be disregarding the rule articulated in MPEP §2113 (cited above) that the structure implied by the process steps should be considered.

As described in the specification, the cells of the invention are cultured in GM-CSF, which was surprisingly found to promote the proliferation *in vitro* of precursor dendritic cells. These proliferating precursors can be used to provide as large populations of antigen-activated dendritic cells, as claimed. The claimed cells are not merely isolated from blood like Pancholi’s cells but are produced by a particular process that imparts to them at least two significant and unexpected differences. First, because the claimed dendritic cells are derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells, they are produced in larger quantities than is possible by mere isolation of dendritic cells from blood. This feature

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of the invention overcomes the previously existing problem of not being able to obtain sufficient quantities of dendritic cells for clinical treatment. A second advantage is that dendritic cells prepared according to the claimed methods are more effective at presenting antigen to T cells *in vitro*. Particularly, results obtained with dendritic cells prepared according to the claimed methods show significant stimulation of T cells at a dendritic cell to T cell (“DC:T”) ratio of 1:1000. This is shown, for example, in Figure 15A, which demonstrates that T cells respond to stimulation by immature or mature BCG-pulsed dendritic cells prepared according to the methods of the invention at DC:T cell ratios of 1:100 and 1:1000. In contrast, Pancholi’s DCs show no stimulation of T cell response at a much lower DC:T ratio of 1:100, and stimulation was only detected at DC:T ratios of 1:50 and above (see Figure 2b). This difference—1:1000 versus 1:50—represents an approximately 20-fold difference in the DC:T ratio found to show stimulation above background levels.

The Examiner’s Answer states that Pancholi’s “Figure 2(a) shows that the dendritic cells were better stimulators of T cells than were monocytes/macrophages.” Appellants disagree with this conclusion; the figure legend indicates that the cells in Figure 2(a) were “partially purified” whereas those in Figure 2(b) were purified by cell sorting. In view of the different results obtained, the significance of the results from Pancholi’s “partially purified” cells is unclear but seems likely to be a result of some contamination with irrelevant cells.

The Examiner’s Answer further appears to indicate that no comparison of results from different experiments is possible. Appellants respectfully disagree that no comparisons can be made. One of skill in the art could reasonably compare the DC:T ratio at which each set of experiments detected stimulation above background levels and conclude from the 20-fold difference that the cells shown in Figure 15A of the present application are significantly better stimulators of T cells than the cells reported by Pancholi. Furthermore, the Examiner’s approach to this issue—that results can only be compared when experiments are done side-by-side in the same laboratory—has the practical effect of mandating that Applicants conduct extensive and very expensive experiments. This would be unduly burdensome and further is unnecessary here to draw the simple conclusion that the cells of Figure 15A are significantly better than Pancholi’s cells in their ability to stimulate T cells.

In view of the above, Appellants conclude that cells of the present invention are more effective at presenting antigen to T cells *in vitro* than the cells taught by Pancholi and are

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therefore different from the cells taught by Pancholi. Because the claimed cells are different from the cells of the reference, the reference would not anticipate the claims even if it were prior art. Accordingly, this rejection should be reversed by the Board.

35 U.S.C. §103—Obviousness (“C”)

In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the invention as a whole would have been obvious. See, *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782 (Fed. Cir. 1983). When assessing the patentability of product-by-process claims over the prior art, **the structure implied by the process steps should be considered, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.** See *In re Garner*, 412 F.2d 276, 279 (CCPA 1979). “[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art.” *In re Fritch*, 972 F.2d 1260, 1265 (Fed. Cir. 1992). “Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR Int’l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007) at 417–418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)).

Appellants respectfully submit that in applying the cited references to the claims, the Examiner appears to be disregarding most of the claim limitations. The present claims specify dendritic cells derived from an *in vitro* culture of proliferating dendritic cell precursors. This is the claimed product. The claims further specify a process by which that product is made. MPEP § 2113, cited in the Examiner’s Answer, clearly states that “determination of patentability is based on the product itself.” Here, the product is not merely dendritic cells, but dendritic cells arising from a specific type of culture. Moreover, the Examiner appears to be disregarding the rule articulated in MPEP §2113 (cited above) that the structure implied by the process steps should be considered.

Further, Appellants respectfully disagree with this rejection because none of the references, nor any combination thereof, teaches any of: the claimed compositions; the starting material used to make the claimed compositions; or the method steps that are necessary to

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produce the claimed compositions. None of the references, either alone or in any combination, teach or suggest that dendritic cell precursors can be cultured *in vitro* in the presence of GM-CSF to produce an enriched and expanded population of proliferating dendritic cell precursors that can in turn be used to produce a large population of mature dendritic cells expressing modified antigen.

The Examiner's Answer states that "[i]t would seem that GM-CSF's role in 'maturation' would provide sufficient motivation for including GM-CSF in a dendritic cell culture for the production of mature dendritic cells." However, a role of GM-CSF in maturation would not provide motivation for adding GM-CSF to a dendritic cell culture such as that of Inaba without some suggestion that those cells were immature, which is absent in the cited references. Further, simply adding GM-CSF to a dendritic cell culture such as that of Inaba's would not, without much more, result in the claimed invention.

The claims are drawn to an *in vitro* composition of cells derived from an *in vitro* culture of an enriched and expanded population of proliferating precursors by a method comprising: culture in GM-CSF, which surprisingly was found to promote that proliferation; further, these cells are cultured *in vitro* in the presence of antigen and express modified antigen. The claimed cells differ from previously reported cells, for example, in their ability to take up antigen even after extended periods of culture. In contrast, the fresh spleen cells of the Inaba reference can only take up antigens for a short time and lose this ability in culture. Indeed, the Examiner previously withdrew an obviousness rejection over the cited Inaba reference for the stated reason that "an objective and quantifiable difference between the DCs of the prior art and the DCs of the instant claims was established (the inability of the DCs of Inaba *et al.* to capture antigen after several days of culture)" (see the Final Office Action of November 18, 2008, page 5). Because Inaba's cells lose the ability to take up antigen, they cannot give rise to enriched and expanded cell populations which then express modified antigen to which they have been exposed *in vitro*, as required by the present claims. Because the cells of the present invention can take up antigen after being cultured for many days, they provide enriched and expanded cell populations in clinically useful quantities, a benefit resulting from Appellants' innovative step of culturing the cells in GM-CSF so as to obtain proliferating dendritic cell precursors. Thus, the claimed compositions provide a number of advantages that result from the novel methods of their production which are not taught or suggested by the prior art.

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Another unexpected advantage of the claimed invention is that, because the claimed cells are derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells, they are produced in larger quantities than is possible by mere isolation of dendritic cells from blood. None of the cited references teaches or suggests that this is possible. This feature of the invention overcomes the previously existing problem of not being able to obtain sufficient quantities of dendritic cells for clinical treatment.

In summary, as discovered by Appellants, culture of dendritic cell precursors in GM-CSF is essential to the development of *in vitro* cultures of proliferating precursor cells and provides a number of advantageous properties to the resulting dendritic cells, including dendritic cells that have been cultured *in vitro* in the presence of an antigen to produce mature dendritic cells expressing modified antigen as required by the claims. None of the cited references teaches or suggests this critical feature of the methods that produce the claimed cells.

Accordingly, for these reasons, and for the reasons discussed in the Appeal Brief, Appellants respectfully submit that the claims are not obvious over the cited references and request that the Board reverse this rejection.

35 U.S.C. §112, Second Paragraph—Indefiniteness (“E”)

35 U.S.C. §112, second paragraph is satisfied if “one skilled in the art would understand the bounds of the claim when read in light of the specification.” *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). In view of the explicit statement in the claim regarding the use of a method and the proper use of active verbs and punctuation, Appellants believe the claim meets the requirements for clarity under 35 U.S.C. § 112, second paragraph. The grounds for the rejection—that the lack of indentation of the method steps renders the claim indefinite—does not appear to have any basis in the statute itself. Further, it is unclear to Appellants that a more vertical and differently spaced arrangement of the claim would have any effect on the meaning or construction of the claim, and Appellants are unaware of any case law construing a claim based on its indentation or lack thereof. Accordingly, Appellants respectfully request that this rejection be reversed by the Board.

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CONCLUSION

For the reasons discussed above, the Examiner's rejections are improper and should be reversed by the Board. Appellants submit that the pending claims are in condition for allowance and earnestly solicit an early notice to that effect.

Respectfully submitted,



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